REMARKS

Reconsideration of this application is respectfully requested.

I. Status of the Claims

With entry of this amendment, claims 32, 33, and 68-92 are pending. Claims 1-31 and 34-67 were previously cancelled. Applicant has amended claim 32 by deleting the terms "modulating" and "modulate" and inserting "increasing" and "increase." Support for this amendment can be found in paragraph [0116] beginning on page 31.

Applicant presents new claims 74-92. Support for these claims can be found in paragraphs [0115-0116] beginning on page 30 and in Examples 9 and 10. No new matter is presented.

II. The Claimed Methods Are Enabled

The Office rejects claims 32, 33, and 68-73 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Office Action, p. 3. The Office admits that the claims are "enabling for increasing the concentration of tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin (TTC) in neuromuscular junction (NMJ) by injecting brain derivated neurotrophic factor (BDNF), GDNF or neurotrophin (NT 4) into Levator auris longus (LAL) muscle or gastrocnemious muscle of mice." *Id.* (see new claims 87-92). However, the Office asserts that the specification "shows that BDNF, GDNF and NT-4 only 'increases' the concentration of tetanus toxin or a fusion protein comprising TTC in neuromuscular junction (NMJ). *Id.* at 4-5. The Office concludes that, because the specification defines "modulate" as both increasing and decreasing, and the specification "fails to provide enabling disclosure for 'decreasing'

the neuronal transport of tetanus toxin or TTC by using BDNF, GDNF, or NT-4" claim 32 and its dependent claims are not enabled. *Id.* at 5.

Without acquiescing to the rejection, and solely to advance prosecution, Applicant has amended claim 32 by deleting "modulate" and inserting "increase." Claims 33 and 68-73 depend from claim 32. Applicant respectfully requests that the Office withdraw the rejection.

The Office rejects claims 32 and 33 because they allegedly "read on only administering BDNF, GDNF or NT-4 to a neuron but NO tetanus toxin or fusion protein comprising TTC is administered." Office Action, p. 5. The Office asserts that "[t]he specification fails to provide adequate guidance and evidence for how to 'modulate' neuronal transport of tetanus toxin or TTC without the presence of tetanus toxin or TTC." *Id.*

Applicant respectfully traverses. A claim should be given its broadest reasonable interpretation. *See* M.P.E.P. § 2111. Here, amended claim 32 recites "a method of increasing the transport in a neuron of a tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin." Accordingly, it is clear from the plain language of the claim that the method modulates the transport of the recited molecules in a neuron. Whether the neurotrophic factors are administered before or after administration of the tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin, the neurons of the claimed method comprise those molecules when the modulation occurs. To interpret claim 32 to include neurons lacking tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin is to read elements out of the claim.

Applicant respectfully submits that such a reading is not the broadest reasonable interpretation but is unreasonably overbroad. Applicant respectfully requests that the Office withdraw the rejection.

III. The Claimed Methods Are Not Obvious

The Office rejects claims 32, 33, and 68-73 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Stoop *et al.*, "Synaptic modulation by neurotrophic factors: differential and synergistic effects of brain-derived neurotrophic factor and ciliary neurotrophic factor," Journal of Neuroscience 16: 3256-64 (1996) ("Stoop"), in view of Miana-Mena *et al.*, "Neuronal activity-dependent membrane traffic at the neuromuscular junction," Proc. Natl. Acad. Sci. 99: 3234-39 (2002) ("Miana-Mena") and Poo, M. "Neurotrophins as synaptic modulators," Nature Reviews 2: 24-32 (2001) ("Poo"). Office Action, p. 6.

According to the Office, Stoop "teaches extracellular application of brain-derived neurotrophic factor (BDNF) to developing neuromuscular junctions in Xenopus nerve-muscle cultures resulted in an increase in the frequency of spontaneous synaptic currents and the amplitude of nerve-evoked synaptic current, and an increase in presynaptic cytosolic Ca^{2+}. Office Action, pp. 6-7.

The Office admits, however, that "Stoop does not teach neurotrophin, such as BDNF, GDNF, and NT-4, can stimulate neuronal transport of tetanus toxin or TTC. *Id.* at 7. But the Office alleges that "Miana-Mena teaches injecting TTC-lac fusion protein intramuscularly and shows that intracellular and transneuronal traffics of the fusion

protein on both sides of the synapse are strongly dependent on presynaptic neural cell activity." *Id.*

The Office also alleges that "Poo teaches that 'synaptic activity regulates the synthesis, secretion and action of neurotrophins, which can in turn induce immediate changes in synaptic efficacy and morphology.'" *Id.* The Office concludes that "[i]t would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to use BDNF, NT-4 or GDNF to modulate neuronal transport of tetanus toxin or TTC in neuromuscular junction," and that the skilled artisan would have had a reasonable expectation of success. *Id.* at 7-8.

Applicant respectfully traverses and submits that the rejection fails to establish *prima facie* obviousness. To determine the obviousness or non-obviousness under 35 U.S.C. § 103 the Examiner must make basic factual inquiries, including (1) determining the scope and content of the prior art, and (2) ascertaining the differences between the prior art and the claims in issue. *See Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1966). Unexpected results indicate that the claimed invention is likely non-obvious. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007). Similarly, the "rationales" described in the recent Guidelines for examiners require a finding that the combination, substitution, improvement, or choice among alternatives produced predictable results. *See Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc.* 72 Fed. Reg. at 57529.

Applicant respectfully submits that, upon consideration of the references as a whole as required by *Graham*, the Office has not established a *prima facie* case of obviousness.

The pending claims recite BDNF, GDNF, and NT-4, but not NGF, NT-3, or CNTF. That is because the empirical evidence in the specification demonstrates that BDNF, GDNF, and NT-4, increase the localization of GFP-TTC at the neuromuscular junction, but NGF, NT-3 and CNTF fail to do so. *See, e.g.,* Specification, paragraph [0115]. Prior to this discovery by Applicant, there was no indication that only certain neurotrophic factors can increase the transport in a neuron of a tetanus toxin or a fusion protein as claimed. And none of the cited documents suggest that only GDNF, NT-4, and CNTF exhibit that property, or that is was possible for the skilled artisan to predict which of the neurotrophins would increase transport as claimed.

Indeed, Stoop groups all of the neurotrophic factors together as if they all have the same activity, stating "Brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and NT4/5, members of the neurotrophin family, promote motor neuron survival *in vitro* and rescue motor neurons from naturally occurring or axotomy-induced cell death." Stoop, p. 3256, col. 1. Stoop also reports that CNTF and NT-3 have similar potentiation effects. *Id.* at col. 2. Accordingly, Stoop does not teach that certain neurotrophins would increase transport as claimed, and one of skill in the art could not have predicted that BDNF, NT-4, and GDNF, but not NGF, NT-3, or CNTF increase transport as claimed.

Poo is similarly limited because it also groups the neurotrophins together under the assumption that they all have the same activity. Poo describes the neurotrophins as "NTs" and uses this term to refer to the neurotrophin's supposed common activity, stating "[s]ynaptic modulation of NTs depends on a cytoplasmic signal-transduction cascade, whose efficacy may be influenced by the presence of electrical activity in the neuron." Poo, p. 28, col. 2. Thus, Poo also fails to lead the skilled artisan to the specific neurotrophins recited in the claims.

Miana-Mena does not cure the deficiencies of Stoop or Poo, because it does not disclose the recited neurotrophins or that BDNF, NT-4, and GDNF increase the internalization of the tetanus toxin or fusion protein as claimed. Accordingly, Applicants respectfully submit that the documents cited by the Office do not render the claimed methods obvious because they fail to show that the skilled artisan would have had predictable success with any given neurotrophin, and do not provide any reason why one of skill in the art would have chosen BDNF, NT-4, and GDNF from among the class of neurotrophins.

Applicant respectfully submits that the Office has failed to establish *prima facie* obviousness of claim 32. Claims 33 and 68-73 ultimately depend from claim 32. Thus, claims 33 and 68-73 are non-obvious for at least the reasons that claim 32 is non-obvious.

Applicant respectfully requests that the Office withdraw the rejection of claims 32, 33, and 68-73.

IV. Priority

The Office asserts that the claimed subject matter "has not been disclosed by Application Nos. 09/816,467, 09/129,386, 60/055,615 and 60/065,236," and that "the effective filing date of the instant application" is September 16, 2003. Office Action, p. 8.

Applicants respectfully traverse. Benefit of priority of each of Application Nos. 09/816,467, 09/129,386, 60/055,615 and 60/065,236 has been claimed for this application, and each of those applications has been incorporated by reference in their entireties.

V. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: James P. Kastenmayer

James P. Kastenmayer
Reg. No. 51,862
Phone: 202-408-4118
Fax: 202-408-4400
E-mail:
jim.kastenmayer@finnegan.com